REMARKS

The Office Action of April 23, 2008 provides examination of claims 1, 3-6, 8, 15-19, 25, 26, 55, 56, 58 and 59, claims 9-14, 20-24, 27-54, 57, 60 and 61 being withdrawn from consideration following restriction of the claims.

Claims 6 and 8 are amended to correct typographical errors arising due to "track changes" errors.

Claims 15, 16, 18-20 and 23 are amended to correct dependency to be dependent upon a pending claim.

Claim 55 is amended to recite that the subject matter comprises "an isolated polynucleotide". Support for this amendment is provided in the specification at, for example, page 17, lines 35-37.

Restriction maintained

The Examiner takes a position that Applicants have received an Office Action on the merits of those claims reciting reduction or ablation of expression of M2-2 protein of HMPV, and therefore examination is limited to such embodiments. Applicants agree that an examination of the merits of this embodiment has been provided, but assert further that such is consistent with their assertion that the present restriction requirement is improper, but that election of species is the correct way to consider all of the embodiments recited in the claims. That is, once the instantly examined species is found allowable, the Examiner should consider the additional species recited in the claims so as to determine if the full scope of the generic claim 1 is patentable.

Rejection under 35 USC section 112, second paragraph

Claims 15-19, 58 and 59 are rejected under 35 USC § 112, second paragraph, as being dependent upon a rejected claim. Claims 15, 16, 18-20 and 23 are amended to be dependent upon claim 1, thus overcoming this rejection.

Rejection under 35 USC § 101

Claim 55 is rejected under 35 USC § 101, as allegedly reading upon a product of nature. While Applicants do not particularly agree, claim 55 is amended to recite that the expression vector is an "isolated polynucleotide", thus overcoming this rejection.

Rejection under 35 USC § 112, first paragraph - written description

Claims 1, 3-6, 8, 15-19, 25, 26, 55, 56, 58 and 59 are rejected under 35 USC § 112, first paragraph, for alleged lack of written description support by this specification. This rejection is respectfully traversed, reconsideration and withdrawal thereof are requested.

The Examiner asserts that the specification fails to describe an adequate number of species, only two being specifically exemplified by working example, of the invention to support a generic claim. The Examiner's position can be summarized by an assertion that the specification does not adequately describe what portions of the M2-2 gene can be changed with retention of the desired phenotype of attenuated replication. (*E.g* "The specification fails to provide structural features of the variant proteins and the biological function of the variant proteins was unpredictable at the time of the invention (discussed below). The specification fails to provide guidance for whether those variant proteins could result in the phenotypic change as recited in the claims.", bridging pp. 5-6 of the Office Action.) Such an assertion reveals that the basis for this rejection is merely USPTO policy against the issuance of broad, generic claims in the recombinant DNA arts, rather than the careful consideration of the claimed invention demanded by case law and the Manual of Patent Examining Procedure. (See, *e.g In re Smith*, 173 USPQ 679 (CCPA 1972), *In re Wertheim*, 191 USPQ 90 (CCPA 1976) and *Enzo Biochem, Inc. v. Gen-Probe, Inc.* 63 USPQ2d 1609 (Fed. Cir. 2002), and MPEP 2163(II)(A).

That is, the present invention relates to ablation of activity of the M2-2 protein, resulting in a phenotype of attenuation of replication and heightened sensitivity of the HMPV to interferon. Applicants do not need to describe mutations that provide for retention of M2-2 activity, and the specification describes a number of types of mutations that ablate or reduce expression of the M2-2 gene. For example, partial or complete deletion of the gene, introduction

of stop codons into the coding sequence, introduction of a frame-shift mutation into the M2-2 gene, alteration of the translation start signal are all described. See, *e.g* page 36, line 30 to page 37, line 13. Such mutations are known in the art to result in ablation of gene expression and this is what is presently claimed. Plainly the specification does describe the ways in which the invention can be implemented, and these ways are easily envisioned by one of ordinary skill in the art. Accordingly, the instant rejection should be withdrawn.

Rejection under 35 USC § 112, first paragraph - enablement

Claims 1-8, 15-19, 25, 26, 55, 56, 58 and 59 are rejected under 35 USC 112, first paragraph, for alleged lack of enabling disclosure by the specification. This rejection is respectfully traversed, reconsideration and withdrawal thereof are requested.

The Examiner admits that claims of the scope such that the M2-2 ORF is lacking from the viral genome are enabled. The Examiner goes on to argue though that claims of scope such that the M2-2 ORF is only partially deleted or includes one or more nucleotide substitutions that reduce or ablates expression of the M2-2 ORF are not enabled.

Applicants reiterate that they have difficulty understanding how this argument can be sustained in view of the Examiner's admission. In particular the specification well-establishes that M2-2 is a gene important for controlling the replication of HMPV. Complete deletion of the M2-2 ORF results in an attenuated phenotype of the virus. One of ordinary skill in the art, especially after reading the present specification, would understand that mutations in the viral genome that result in a decline in activity of the M2-2 ORF would also result in attenuation of viral replication, although possibly to a degree different than that accomplished by complete deletion of the M2-2 ORF.

The Examiner is further reminded that the specification includes description of how to make any particular mutation in the HMPV viral genome and how to test such mutated viruses for a suitable degree of attenuation of replication. See, for example, description beginning at

page 28, line 35, and continuing through the end of page 35 at least. See also, for instance, Example 2 beginning at page 65, line 30, which describes production of an HMPV virus including a GFP reporter gene that can be used to easily monitor the level of replication of a virus including any particular mutation or combination of mutations, Example 3 beginning at page 74, line 25, describing the development of a number of mutated HMPV viruses having specified mutations imparting desired phenotypes to the virus, and Example 5 beginning at page 93, line 27 demonstrating the analysis of viral phenotype, including replication levels, in experimental animals.

Furthermore, the Examiner makes a number of arguments related to unpredictability in the art as to how variation in the structure of a protein affects activity of the protein. Again, the instant invention relates to ablation of activity of a protein, and the various ways in which this can be accomplished are described in the specification and well-known in the art to be effective. Once again, the presentation of this entire line of argument reveals that the Examiner is merely reciting policy put in place by the USPTO rather than carefully considering the facts presented by the instant application. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988) at page 1404 ("The determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness, having due regard for the nature of the invention and the state of the art. *Ansul Co. v. Uniroyal, Inc.* 448 F.2d 872, 878-79; [169 USPQ 759, 762-63] (2d Cir. 1971), *cert. denied*, 404 U.S. 1018 [172 USPQ 257] (1972) ... Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations.").

Finally, it has been established in U.S. case law that a disclosure that provides to the public a starting material that provides the opportunity to make variants in the structure of the invention, such as the cloned DNAs of the complete genome of HMPV of the present application, together with description of tests for operability of the invention for its intended purpose (which may be provided by the prior art as well), fulfills the requirements for

enablement even in the face of a high degree of unpredictability in the art. See, *e.g Ex parte Kubin*, 83 USPQ2d 1410 (BPAI 2007).

The present specification meets the above-described standards, and therefore for at least this reason, the instant rejection should be withdrawn.

Rejection under 35 USC § 103(a)

Claims 1-4, 6-8, 15, 16, 18, 25, 55 and 56 are rejected under 35 USC §103(a) as being unpatentable over Bermingham et al. (1999) in view of van den Hoogen et al. (2001) and van den Hoogen et al. (2002). Also, claims 1 and 3-5 stand rejected under 35 USC § 103(a) as being unpatentable over Bermingham et al. (1999) in view of van den Hoogen et al. (2001), van den Hoogen et al. (2002) and further in view of Ludin (1996). These rejections are respectfully traversed, reconsideration and withdrawal thereof are respectfully requested.

The Examiner considers Dr. Collins' Declaration, but finds it unpersuasive "because of the reasons set forth above." (Page 21, lines 16-17 of the Office Action.) However, no "reasons" are set forth above this sentence in the Office Action. Instead, there is merely an explanation of the Examiner's reasons why the prior art is asserted and a summary of the Examiner's understanding of the Dr. Collins' Declaration. The Examiner is requested to clarify his reasons why Dr. Collins' Declaration is considered unpersuasive. The Examiner is cautioned against substituting his judgment for that of Dr. Collins about the facts presented in the Declaration and any conclusions Dr. Collins might draw from those facts. See, *e.g In re Katzschmann* 146 USPQ 66 (CCPA 1965).

In particular, the Examiner repeatedly asserts that conclusions about the biology of HMPV can be drawn based on analogy to RSV. Dr. Collins' Declaration specifically states that such conclusions are not reached properly due to lack of similarity between the two viruses and because the properties of the two kinds of virus are sufficiently distinct that methods for "rescue" of RSV from recombinant cDNA vectors did not work for rescue of HMPV viruses.

The Examiner does explain that, "Whether M2-2 protein of HMPV would have the same biological function as that of RSV and the result of attenuated M2-2 of HMPV would be predictable are irrelevant because the claims do not recite the resulting phenotype changes of the attenuated HMPV ...." This is incorrect. Claim 1, the independent claim presently examined, recites that the virus is one that is replication competent, but attenuated.

The Examiner does make an assertion at page 22 of the Office Action that the van den Hoogen (2001) reference provides a complete sequence of a genome of a HMPV isolate and that van den Hoogen (2002) provides a complete genomic map of the N, P, L and M2(ORF2) ORFs. The Examiner further criticizes Dr. Collins' Declaration in that,

> It is unclear why the sequence disclosed by van den Hoogen is considered a partial sequence of the genome in Dr. Collins' Declaration. Dr. Collins' Declaration states that the sequence disclosed by van den Hoogen lacks key promoters but fails to point out what promoter is lacking and that no viable virus can be produced by one of ordinary skill in the art. The HMPV isolate 00-1 is viable virus and was propagated in tertiary monkey kidney cells. With the complete genomic sequence of HMPV at hand and known technology in making recombinant viruses and growing viable HMPV viruses, it would be obvious to one of ordinary skill in the art to practice the invention as claimed in the instant application.

In reply, Applicants submit that, as to van den Hoogen 2001, this reference shows part of a putative leader region (Fig. 3A) and part of a putative intergenic region (Fig. 3B), but no other nucleotide sequence. Fig3C, D, E, and F show predicted amino acid sequences for the proposed N, P, M and F genes, but no nucleotide sequences. So, that reference describes only a very small part of the genome. The van den Hoogen 2002 reference does provide a continuous sequence of the N, P, M, F, M2, SH, G, and L genes and intergenic sequences, but does not identify the termini or provide direct sequence analysis of any potential promoters that would be expected to be located at the termini (and now indeed are known to be located there).

Regarding the putative leader region, the authors have underlined the first 15 nt in Fig. 3A of van den Hoogen 2001 and commented: "Note that the underlined sequence in A refers to the primer used for PCR amplification, and therefore does not necessarily reflect the actual hMPV leader sequence". Similarly, in van den Hoogen 2002, the authors indicate "it should be noted that the sequence of the genomic termini reflects primer sequences and therefore these parts of the genome are still uncertain with respect to size and sequence". Their Genbank entry similarly is incomplete for both genomic termini. The reason for this uncertainty is that the RT PCR used primers designed from the termini of the genome of avian pneumovirus (APV, also known as turkey rhinotracheitis virus and presently also known as avian metapnemovirus, AMPV). APV was used to design these primers because it was thought to be the closest relative to hMPV, which now is known to indeed be true. However, it is well known that primers can hybridize and direct amplification in situations containing one or multiple mis-matches, especially in RT reactions since these cannot tolerate high temperatures that can increase fidelity. Thus, one could not exclude that the hMPV sequence in this region might contain nt differences. Indeed, one could not reliably conclude that these sequences represented the hMPV termini at all. This is clearly noted in the authors' second caveat above ("with respect to size and sequence").

The idea that this would be an authentic concern by workers in the field is illustrated, for example, by Randhawa et al J Virol 1997 71:9849, in which the genome termini of APV were sequenced by direct methods (in contrast to the indirect methods of van den Hoogen et al, but similar to the direct methods in the present application). Even so, Randhawa et al. felt sufficiently unsure about the veracity of the sequence that they felt compelled to use a mini-replicon system to demonstrate that those APV sequences indeed were functional as promoters. This formed the basis of an entire manuscript that was published in a premier journal, demonstrating that it was not a trivial finding. Similarly, the present inventors directly sequenced the hMPV viral genome termini and confirmed their functionality by constructing complete recombinant virus and verifying a wild-type phenotype in cell culture, in rodents, and in a non-human primate model.

Thus, neither the 5' nor 3' terminus of hMPV was mapped or sequenced by van den Hoogen. Furthermore, one could not attempt to presumptively identify contiguous sequence (adjacent to the primer sequences) as being promoter-related by the expedient of sequence alignment with related viruses because there is too much sequence divergence. Thus, van den Hoogen did not provide critical sequence at the two ends of the genome, and did not exclude the possibility of additional genes.

Even if one accepted that there are no additional hMPV genes and that the termini were correctly identified and sequenced by van den Hoogen, there are three errors in their predicted sequence of these critical promoters. The leader sequence provided by van den Hoogen (ACGAGAAAAAAA) is incorrect at position 4 (underlined), which should be C. The trailer sequence (ACGAGAAAAAAA) is incorrect at positions 4 and 5 (underlined), which should be GC. It is well known that the first 10-12 nt at both termini are important parts of the promoters of negative-stranded RNA viruses (*e.g*, Fearns et al, 2002, J Virol 76:1663). The analysis of Fearns et al (performed with an HRSV mini-replicon) supports the expectation that it would be highly unlikely that a synthetic genome containing three errors in this critical sequence would be functional, particularly in infectious helper-independent virus. Furthermore, faced with an inability to recover replication-competent virus, one would have no guidance as to which residues might be at fault.

Applicants also note that, while van den Hoogen et al do provide sequences for a number of hMPV genes and proteins, there is no evidence that these sequences encode functional proteins. It is not unusual to have errors in cDNA clones, and providing a correct sequence of at least one working model is needed to identify genetic elements required to establish a reverse genetics system.

The fact that the biological virus is viable in cell culture is irrelevant to the need to know its complete sequence in order to make viable recombinant derivatives utilizing the present invention. Given that the critical promoter sequences provided by van den Hoogen contained

three errors, one of ordinary skill in the art would have no ready means for detecting and correcting these errors except by making the present invention.

Applicants submit that the standing rejections for obviousness are overcome and respectfully request that they be withdrawn.

Applicants submit that the present application well-describes and enables patentable subject matter. The favorable actions of withdrawal of the standing rejections and allowance of the pending claims are respectfully requested.

Should there be any outstanding matters that need to be resolved in the present application, the Examiner is respectfully requested to contact Mark J. Nuell, Reg. No. 36,625 at the telephone number of the undersigned below, to conduct an interview in an effort to expedite prosecution in connection with the present application.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.14; particularly, extension of time fees.

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Respectfully submitted,

By _____
Mark J. Nuell
Registration No.: 36,623
BIRCH, STEWART, KOLASCH & BIRCH, LLP
12770 High Bluff Drive, Suite 260
San Diego, California 92130
(858) 792-8855
Attorney for Applicants